AF/1634

TRANSMITTAL OF APPEAL BRIEF			Docket No. OKA-0027
In re Application of: Tomoko Nakayama, et al.			
Application No. 09/843,819-Conf. #9941	Filing Date April 30, 2001	Examiner S. Sakelaris	Group Art Unit 1634
Invention: METHOD FOR SYNTHESIS OF NUCLEIC ACIDS			

TO THE COMMISSIONER OF PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed: July 9, 2003 .

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[X] The Director is hereby authorized to charge any additional fees that may be required or credit any overpayment to Deposit Account No. 18-0013 .
This sheet is submitted in duplicate.

Dated: September 9, 2003

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Docket No.: OKA-0027
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Tomoko Nakayama, et al.

Application No.: 09/843,819 Confirmation No.: 9941

Filed: April 30, 2001 Art Unit: 1634

For: METHOD FOR SYNTHESIS OF NUCLEIC ACIDS Examiner: S. Sakelaris

APPELLANT'S BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This brief is in furtherance of the Notice of Appeal, filed in this case on July 9, 2003.

The fees required under § 1.17(f) and any required petition for extension of time for filing this brief and fees therefor, are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief is transmitted in triplicate.

This brief contains items under the following headings as required by 37 C.F.R. § 1.192 and M.P.E.P. § 1206:

I. Real Party In Interest
II Related Appeals and Interferences
III. Status of Claims
IV. Status of Amendments
V. Summary of Invention
VI. Issues
VII. Grouping of Claims
VIII. Arguments
IX. Claims Involved in the Appeal
Appendix A Claims

I. REAL PARTY IN INTEREST

The real party in interest for this appeal is:

Shimadzu Corporation of Kyoto, Japan. An assignment of all rights in the present application to Shimadzu Corporation of Kyoto, Japan was executed by the inventors and recorded by the U.S. Patent and Trademark Office at **reel 011749, frame 0830.**

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 11 claims pending in application. Claims 1-11 stand finally rejected, and no claims are currently allowed.

Accordingly, the Appellants hereby appeal the final rejection of claims 1-11, which are presented in the Appendix.

B. Current Status of Claims

1. Claims canceled: 12

2. Claims withdrawn from consideration but not canceled: None

3. Claims pending: 1-11

4. Claims allowed: None

5. Claims rejected: 1-11

C. Claims On Appeal

The claims on appeal are claims 1-11

IV. STATUS OF AMENDMENTS

An Amendment canceling claim 12 without prejudice or disclaimer and amending claims 1-3 was filed subsequent to the first rejection of September 17, 2002 (Paper No. 7). No Amendment after the final rejection of April 9, 2003 (Paper No. 9) that is the subject of this Appeal was filed.

The claims in the Appendix represent the state of the claims as pending.

V. SUMMARY OF INVENTION

The presently claimed invention is a method for synthesis of nucleic acids, especially to a method for synthesis of nucleic acids by means of a polymerase chain reaction (hereinafter abbreviated as a PCR). See page 1, first full paragraph.

The PCR can be carried out by adding a nucleic acid inclusion body in a sample or the sample itself to a reaction solution for gene amplification, if a pH value of a PCR reaction solution is raised or if polyamines are added to the PCR reaction solution. However, it was found that DNA in the sample sometimes could not be efficiently amplified depending on a region to be amplified, even if above-mentioned method was used. In addition, it is known that the amplification is difficult to be conducted in the case that a content of guanine (G) and cytosine (C) (hereinafter referred to as a GC content) is rich in a

region where gene amplification occurs, even if purified DNA is used for the PCR. Page 3, line 21 to page 4, line 9.

Thus, the present invention provides a method of treatment that is useful in conducting a nucleic acid synthesis procedure capable of directly amplifying an intended nucleic acid in a living body-derived sample without purification steps. Page 4, lines 10-14.

As a result of eager studies, the present inventors found out that nucleic acids in a region in which a GC content is rich could be amplified when a polyhydric alcohol and ammonium sulfate was allowed to be present in a reaction solution. Page 4, lines 15-19.

Namely, the present invention is a method for synthesis of nucleic acids, which comprises: amplifying an intended nucleic acid in a region in which a content of guanine (G) and cytosine (C) is rich in an amplification reaction solution comprising a polyhydric alcohol and ammonium sulfate. Hereinafter, "a region in which a GC content is rich" is referred to as "a GC rich region". Page 5, line 20 to page 5, line 1.

The present invention is the method for synthesis of nucleic acids, which comprises: amplifying an intended nucleic acid in a region in which a content of guanine (G) and cytosine (C) is rich in an amplification reaction solution comprising a polyhydric alcohol and ammonium sulfate. See claim 1.

The present invention is the method for synthesis of nucleic acids wherein a nucleic acid inclusion body from a living body-derived sample or the living body-derived sample itself is added to the amplification reaction solution. Page 5, lines 2-5.

The present invention is the method for synthesis of nucleic acids discussed above wherein the amplifying step comprises adjusting a pH value of the amplification reaction solution to 8.4 or higher if the reaction solution is about 25 °C, and/or adjusting a pH value of the amplification reaction solution to 7.4 or higher if the reaction solution is about 70 °C. Page 5, lines 6-9.

The present invention is the method for synthesis of nucleic acids wherein the polyhydric alcohol is glycerin. Page 5, lines 10-11.

According to the present invention, it becomes possible to amplify nucleic acids in a GC rich region efficiently in direct manner from a sample such as blood containing lots of PCR inhibitory substances without undergoing a process of isolating and purifying the nucleic acids, although it has been known that the PCR in the GC rich region is difficult to be conducted even

if purified DNA is used. It becomes possible by the present invention to conduct synthesis of nucleic acids from a sample more simply, conveniently and rapidly. Further, it becomes also possible to reduce contamination. Page 5, lines 12-22.

VI. ISSUES

The issue presented for consideration in this appeal is as follows:

(1) Whether the Examiner erred in rejecting claims 2-3 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite?

(2) Whether the Examiner erred in rejecting claims 1, 2 and 4-9 under 35 U.S.C. §103(a) as being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe")?

(3) Whether the Examiner erred in rejecting claims 3 and 11 under 35 U.S.C. §103(a) as being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe") and further in view of U.S. Patent No. 5,972,618 ("Bloch")?

(4) Whether the Examiner erred in rejecting claim 10 under 35 U.S.C. §103(a) as being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe") and in further view

of Pomp et al., Organic Solvents as Facilitators of Polymerase Chain Reaction," 10 Biofeedback 58 (1991) ("Pomp") and U.S. Patent No. 5,432,065 ("Fuller")?

VII. GROUPING OF CLAIMS

For purposes of this appeal brief only, and without conceding the teachings of any prior art reference, the claims have been grouped as indicated below:

Claims 2-3 stand or fall separately with respect to the §112 rejection.

Claims 1, 2 and 4-9 stand or fall together with respect to the §103 rejections over Henke in view of Watanabe.

Claim 3 and 11 stand or fall together with respect to the §103 rejections over Henke in view of Watanabe and further in view of Bloch.

Claim 10 stands or falls alone with respect to the §103 rejections over Henke in view of Watanabe and further in view of Pomp and Fuller.

In Section VIII below, Applicant has included arguments supporting the separate patentability of each claim group as required by M.P.E.P. § 1206.

VIII. ARGUMENTS

In the Final Office Action of April 9, 2003, the following rejections were presented by the Examiner:

(i) 35 U.S.C. §112

The Examiner rejected claims 2-3 under 35 U.S.C. §112, second paragraph as allegedly being indefinite.

(ii) 35 U.S.C. §103

The Examiner rejected claims 1, 2 and 4-9 under 35 U.S.C. §103(a) as allegedly being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe").

The Examiner rejected claims 3 and 11 under 35 U.S.C. §103(a) as allegedly being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe") and further in view of U.S. Patent No. 5,972,618 ("Bloch").

The Examiner rejected claim 10 under 35 U.S.C. §103(a) as allegedly being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe") and in further view of Pomp et al., Organic Solvents as Facilitators of Polymerase Chain Reaction," 10 Biofeedback 58 (1991) ("Pomp") and U.S. Patent No. 5,432,065 ("Fuller").

(iii) Other

None

For at least the following reasons, Appellant submits that these rejections are both technically and legally unsound and should therefore be reversed.

(i) 35 U.S.C. §112

The examiner rejected claims 2-3 under 35 U.S.C. §112, second paragraph as allegedly being indefinite. Appellants respectfully disagree, and accordingly, traverse this rejection.

Regarding claim 2, the examiner alleges that "nucleic acid inclusion body" is indefinite because: it is not defined in the claim, the specification does not provide a standard, and there is no fixed definition in the art.

Claim 2 recites a method for synthesis of nucleic acids according to claim 1, wherein a nucleic acid inclusion body from a living body-derived sample or the living body-derived sample itself is added to the amplification reaction solution.

The term "nucleic acid inclusion body" is a compound term based on "nucleic acid" and "inclusion body," the combination referring to the inclusion body (site, location in the cell) for nucleic acid (RNA, DNA) replication. The term is used repeatedly throughout the specification, for example at page 3, line 22, page 8, lines 5, 18 and 21 and page 11, lines 17-18. Appellants believe the term "nucleic acid inclusion body" is clear on its face.

Accordingly, the §112, second paragraph rejection of claim 2 should not be sustained.

Regarding claim 3, the examiner is objecting the examiner alleges that the "and/or" alternative recited in claim 3 is indefinite.

Claim 3 recites a method for synthesis of nucleic acids according to claim 1, wherein said amplifying step comprises adjusting a pH value of the amplification reaction solution to 8.4 or higher if the reaction solution is about 25 °C, and/or adjusting a pH value of the amplification reaction solution to 7.4 or higher if the reaction solution is about 70 °C.

The metes and bounds of claims are not rendered unclear merely because of the presence of alternative language in the claims. The Federal Circuit has held that the word "or"

should be interpreted to mean a choice between one of two alternatives, but not both. See Kustom Signals Inc. v. Applied Concepts Inc., 60 USPQ2d 1133 (Fed. Cir. 2001), cert. denied, 122 S. Ct. 1537 (2002). Expanding on this, it is clear that "and/or" stands for the option of adding the following step to the previous step, or treating the two steps in the alternative. When parsed, Claim 3 clearly recites two situations for adjusting the pH of the amplification reaction solution: 1. adjusting a pH value of the amplification reaction solution to 8.4 or higher if the reaction solution is about 25 °C, and 2. adjusting a pH value of the amplification reaction solution to 7.4 or higher if the reaction solution is about 70 °C. The presence of the coma after the first adjusting language clearly separates the two choices. The phrase "and/or" tells the reader of the claim that choices 1 and 2 can both be performed, or either choice 1 or choice 2 can be performed.

Thus, it is quite clear from the claim, when taken in context, is proper construction, and clear on its face. Accordingly, the §112, second paragraph rejection of claim 3 should not be sustained.

(ii) 35 U.S.C. §103

The Examiner rejected claims 1, 2 and 4-9 under 35 U.S.C. §103(a) as allegedly being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe"). Appellants respectfully traverse this rejection.

Claim 1 recites a method for synthesis of nucleic acids, which comprises: amplifying an intended nucleic acid in a region in which a content of guanine (G) and cytosine (C) is rich in an amplification reaction solution comprising a polyhydric alcohol and ammonium sulfate.

Neither Henke nor Watanabe, alone or in combination, teach or suggest that a polyhydric alcohol and ammonium sulfate are present in an amplification reaction solution together. In fact, it is clear that a person of ordinary skill in the art would not find motivation in

the Henke and Watanabe references to combine their teachings to arrive at such an amplification reaction solution.

Henke essentially teaches away from adding a polyhydric alcohol such as glycerine in some PCR solutions, depending on the nucleic acid to be amplified. Henke teaches (p. 3957) that in a co-amplification of both an antigen's mRNA (GC-rich) and a variant of the antigen's mRNA (also GC-rich) by RT and PCR, 10% glycerine proved ineffective at co-amplification. The amplification of the variant of the antigen's mRNA was optimized when glycerine was added, but the amplification of the antigen's mRNA was depressed. Still further, Henke's PCR process involved isolated gene fragments, and not a more complex nucleic acid inclusion body or an even more complex living body-derived sample. Additionally, Watanabe discloses that genomic DNA was extracted from peripheral lymphocytes (page 17, lines 13 to 14).

Watanabe only makes mention of a PCR process at column 1 of page 17, and column 1 of page 18. In these passages, Watanabe discloses that during a PCR process, 10 mM ammonium sulfate is added to the solution that includes blood samples, and that the ammonium sulfate is greatly effective in terms of improving the efficiency of the process. However, Watanabe clearly fails to teach or suggest the feature of a polyhydric alcohol and ammonium sulfate being present in an amplification reaction solution together.

A person of ordinary skill in the art who reads Henke would actually be steered away from trying to perform PCR using glycerine together with another compound such as ammonium sulfate. Henke teaches that glycerine is not effective at co-amplification PCR, and teaches that betaine improves the co-amplification process when used in place of glycerine. Then, from reading the advantages of using ammonium sulfate in a PCR solution, a person of ordinary skill in the art would, at best, be persuaded to add ammonium sulfate and betaine to a PCR solution for coamplification. However, Watanabe fails to provide any teachings that would overcome a Henke-based presumption that glycerine would be ineffective. When the teachings of the prior art are considered as a whole, there is no motivation found in the references to render claim 1 obvious.

Still further, the Office Action states that Henke and Watanabe "coupled either polyhydric alcohol or ammonium sulfate to the use of DMSO (10%) in an attempt to amplify GC-rich sequences." Page 5, lines 14-15. The examiner then alleges that the "disclosure of each additive's potential for improving the efficiency of PCR involving GC-rich sequences, makes the subsequent combination of such similar, well known additives obvious to one of ordinary

skill in the art." Page 5, lines 16-18. Appellants disagree. As discussed above, if one reference teaches away from using an additive, there can be no obvious working substitution. Still further, this is blatant hindsight reasoning and blueprinting.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, *absent some teaching, suggestion or incentive supporting the combination*. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so. The prior art of record fails to provide any such suggestion or incentive. ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984).

Accordingly, the Examiner has not established a prima facie case of obviousness, the rejection of the claims should not be sustained.

Still further, "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 23 USPQ 2d 1780 (Fed. Cir. 1992). The office action has not established that one of ordinary skill would use ammonium sulfate in place of polyhydric alcohol in Henke. Accordingly, a prima facie case of obviousness has not been established, and the rejection should not be sustained.

The conclusion that this combination would result in the claimed combination is clearly based on Appellants invention and not on the prior art! This form of reasoning is impermissible and is clearly based on improper hindsight reasoning. It is established law that one "cannot use hindsight reconstruction to pick and chose among isolated disclosures in the prior art to deprecate the claimed invention." Ecolochem, Inc. v. Southern California Edison Company, page 23, September 7, 2000 (Fed. Cir.) (citing In re Fine, 837 F.2d 1071, 1075, 5, USPQ2d 1780, 1783 (Fed. Cir. 1988)). "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight." Ecolochem at 24 (citing In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999)). "When a rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references." Ecolochem at 24 (citing In re Rouffet, 149 F.3d 1350, 1355, 47 USPQ2d 1453, 1456 (Fed. Cir. 1988), citing In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987)). Additionally, "defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to

obviousness." Ecolochem at 24 (citing Monarch Knitting Mach. Corp. v. Sulzer Morat Gmbh, 139 F.3d 877, 880, 45 USPQ2d 1977, 1981 (Fed. Cir. 1998)).

Accordingly, a prima facie case of obviousness has not been established, and the rejection should not be sustained.

Furthermore, claims 2 and 4-9, being dependent upon claim 1, are also allowable for the reasons above. Moreover, these claims are further distinguished by the materials recited therein, particularly within the claimed combination. Accordingly, all §103 rejections should not be sustained.

Claims 3 and 11 are rejected as being unpatentable over Henke in view of Watanabe and further in view of U.S. Patent No. 5,972,618 ("Bloch"). Appellants respectfully traverse this rejection.

Claim 3 recites the method for synthesis of nucleic acids according to claim 1, wherein said amplifying step comprises adjusting a pH value of the amplification reaction solution to 8.4 or higher if the reaction solution is about 25 °C, and/or adjusting a pH value of the amplification reaction solution to 7.4 or higher if the reaction solution is about 70 °C.

Claim 11 recites the method for synthesis of nucleic acids according to claim 1, wherein ammonium sulfate is present at a concentration from 20 mM to 100 mM in the amplification reaction solution.

Bloch is provided for teaching an increased pH and concentration of ammonium sulfate in a PCR solution. However, Bloch fails to teach or suggest the use of both ammonium sulfate and a polyhydric alcohol in an amplification reaction solution. Accordingly, Bloch does not make up for the deficiencies of Henke and Watanabe, discussed above. That is, even if the references could be combined, Bloch does not disclose, teach or suggest any teachings that would overcome a Henke-based presumption that glycerine would be ineffective.

Accordingly, a prima facie case of obviousness has not been established, and the rejection should not be sustained.

Furthermore, claims 3 and 11, being dependent upon claim 1, are also allowable for the reasons above. Moreover, these claims are further distinguished by the materials recited

therein, particularly within the claimed combination. Accordingly, all §103 rejections should not be sustained.

Claim 10 was rejected under 35 U.S.C. §103(a) as allegedly being obvious over Henke in view of Watanabe and in further view of Pomp et al., Organic Solvents as Facilitators of Polymerase Chain Reaction," 10 Biofeedback 58 (1991) ("Pomp") and U.S. Patent No. 5,432,065 ("Fuller"). Appellants respectfully traverse this rejection.

Claim 10 recites the method for synthesis of nucleic acids according to claim 7, wherein the aliphatic polyhydric alcohol is ethylene glycol.

Pomp is provided for its teachings of the use of 5 to 20% ethylene glycol in PCR solutions that only used DMSO as an enhancing agent. Since Henke is directed to PCR solutions that could use DMSO, the Examiner's position is that it would be obvious to combine Henke and Pomp to arrive at claim 10. Further, Fuller is provided for its teachings of the use of between 10 and 50% glycerol or ethylene glycol are added to an amplification solution. In any respect, Pomp and Fuller fail to teach or suggest the use of both ammonium sulfate and a polyhydric alcohol in an amplification reaction solution, as recited in claim 1.

Accordingly, Pomp and Fuller do not make up for the deficiencies of Henke and Watanabe, discussed above. That is, even if the references could be combined, Pomp and Fuller do not disclose, teach or suggest any teachings that would overcome a Henke-based presumption that glycerine would be ineffective.

Accordingly, a prima facie case of obviousness has not been established, and the rejection should not be sustained.

Furthermore, claim 10, being dependent upon claim 1, is also allowable for the reasons above. Moreover, this claim is further distinguished by the materials recited therein, particularly within the claimed combination. Accordingly, all §103 rejections should not be sustained.

(iii) Other

None

Conclusion

In view of the foregoing reasons, Appellant submits that the final rejection of claims 1-11 is improper and should not be sustained. Therefore, a reversal of the Final Rejection of April 9, 2003, as to claims 1-11, is respectfully requested.

IX. CLAIMS INVOLVED IN THE APPEAL

A copy of the claims involved in the present appeal is attached hereto as Appendix A. As indicated above, the claims in Appendix A do include the amendments filed by Applicant on December 17, 2002.

Dated: September 9, 2003

Respectfully submitted,

By _____

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 180013 for any such fees; and applicant(s) hereby petition for any needed extension of time.

APPENDIX A

Claims Involved in the Appeal of Application Serial No. 09/843,819

1. (Previously presented) A method for synthesis of nucleic acids, which comprises:

amplifying an intended nucleic acid in a region in which a content of guanine (G) and cytosine (C) is rich in an amplification reaction solution comprising a polyhydric alcohol and ammonium sulfate.

2. (Previously presented) The method for synthesis of nucleic acids according to claim 1, wherein a nucleic acid inclusion body from a living body-derived sample or the living body-derived sample itself is added to the amplification reaction solution.

3. (Previously presented) The method for synthesis of nucleic acids according to claim 1, wherein said amplifying step comprises adjusting a pH value of the amplification reaction solution to 8.4 or higher if the reaction solution is about 25 °C, and/or adjusting a pH value of the amplification reaction solution to 7.4 or higher if the reaction solution is about 70 °C.

4. (Original) The method for synthesis of nucleic acids according to claim 1, wherein the GC content in the GC rich region is 40% or more.

5. (Original) The method for synthesis of nucleic acids according to claim 1, wherein the GC content in the GC rich region is a range from 50% to 70%.

6. (Original) The method for synthesis of nucleic acids according to claim 1, wherein the polyhydric alcohol is selected from the group consisting of an aromatic polyhydric alcohol, an aliphatic polyhydric alcohol and an ether glycol.

7. (Original) The method for synthesis of nucleic acids according to claim 6, wherein the aliphatic polyhydric alcohol is selected from the group consisting of ethylene glycol, propylene glycol, butanediol, hexanediol, octanediol, glycerin, sorbitan, trimethylolpropane and neopentyl glycol.

8. (Original) The method for synthesis of nucleic acids according to claim 7, wherein the aliphatic polyhydric alcohol is glycerin.

9. (Original) The method for synthesis of nucleic acids according to claim 8, wherein glycerin is contained in a range from 2.5% to 20% by volume in the amplification reaction solution.

10. (Original) The method for synthesis of nucleic acids according to claim 7, wherein the aliphatic polyhydric alcohol is ethylene glycol.

11. (Original) The method for synthesis of nucleic acids according to claim 1, wherein ammonium sulfate is present at a concentration from 20 mM to 100 mM in the amplification reaction solution.

12. (Cancelled)

Docket No.: OKA-0027
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Tomoko Nakayama, et al.

Application No.: 09/843,819 Confirmation No.: 9941

Filed: April 30, 2001 Art Unit: 1634

For: METHOD FOR SYNTHESIS OF NUCLEIC ACIDS Examiner: S. Sakelaris

APPELLANT'S BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This brief is in furtherance of the Notice of Appeal, filed in this case on July 9, 2003.

The fees required under § 1.17(f) and any required petition for extension of time for filing this brief and fees therefor, are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief is transmitted in triplicate.

This brief contains items under the following headings as required by 37 C.F.R. § 1.192 and M.P.E.P. § 1206:

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II Related Appeals and Interferences
III. Status of Claims
IV. Status of Amendments
V. Summary of Invention
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Appendix A Claims

I. REAL PARTY IN INTEREST

The real party in interest for this appeal is:

Shimadzu Corporation of Kyoto, Japan. An assignment of all rights in the present application to Shimadzu Corporation of Kyoto, Japan was executed by the inventors and recorded by the U.S. Patent and Trademark Office at **reel 011749, frame 0830.**

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 11 claims pending in application. Claims 1-11 stand finally rejected, and no claims are currently allowed.

Accordingly, the Appellants hereby appeal the final rejection of claims 1-11, which are presented in the Appendix.

B. Current Status of Claims

1. Claims canceled: 12

2. Claims withdrawn from consideration but not canceled: None

3. Claims pending: 1-11

4. Claims allowed: None

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C. Claims On Appeal

The claims on appeal are claims 1-11

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An Amendment canceling claim 12 without prejudice or disclaimer and amending claims 1-3 was filed subsequent to the first rejection of September 17, 2002 (Paper No. 7). No Amendment after the final rejection of April 9, 2003 (Paper No. 9) that is the subject of this Appeal was filed.

The claims in the Appendix represent the state of the claims as pending.

V. SUMMARY OF INVENTION

The presently claimed invention is a method for synthesis of nucleic acids, especially to a method for synthesis of nucleic acids by means of a polymerase chain reaction (hereinafter abbreviated as a PCR). See page 1, first full paragraph.

The PCR can be carried out by adding a nucleic acid inclusion body in a sample or the sample itself to a reaction solution for gene amplification, if a pH value of a PCR reaction solution is raised or if polyamines are added to the PCR reaction solution. However, it was found that DNA in the sample sometimes could not be efficiently amplified depending on a region to be amplified, even if above-mentioned method was used. In addition, it is known that the amplification is difficult to be conducted in the case that a content of guanine (G) and cytosine (C) (hereinafter referred to as a GC content) is rich in a

region where gene amplification occurs, even if purified DNA is used for the PCR. Page 3, line 21 to page 4, line 9.

Thus, the present invention provides a method of treatment that is useful in conducting a nucleic acid synthesis procedure capable of directly amplifying an intended nucleic acid in a living body-derived sample without purification steps. Page 4, lines 10-14.

As a result of eager studies, the present inventors found out that nucleic acids in a region in which a GC content is rich could be amplified when a polyhydric alcohol and ammonium sulfate was allowed to be present in a reaction solution. Page 4, lines 15-19.

Namely, the present invention is a method for synthesis of nucleic acids, which comprises: amplifying an intended nucleic acid in a region in which a content of guanine (G) and cytosine (C) is rich in an amplification reaction solution comprising a polyhydric alcohol and ammonium sulfate. Hereinafter, "a region in which a GC content is rich" is referred to as "a GC rich region". Page 5, line 20 to page 5, line 1.

The present invention is the method for synthesis of nucleic acids, which comprises: amplifying an intended nucleic acid in a region in which a content of guanine (G) and cytosine (C) is rich in an amplification reaction solution comprising a polyhydric alcohol and ammonium sulfate. See claim 1.

The present invention is the method for synthesis of nucleic acids wherein a nucleic acid inclusion body from a living body-derived sample or the living body-derived sample itself is added to the amplification reaction solution. Page 5, lines 2-5.

The present invention is the method for synthesis of nucleic acids discussed above wherein the amplifying step comprises adjusting a pH value of the amplification reaction solution to 8.4 or higher if the reaction solution is about 25 °C, and/or adjusting a pH value of the amplification reaction solution to 7.4 or higher if the reaction solution is about 70 °C. Page 5, lines 6-9.

The present invention is the method for synthesis of nucleic acids wherein the polyhydric alcohol is glycerin. Page 5, lines 10-11.

According to the present invention, it becomes possible to amplify nucleic acids in a GC rich region efficiently in direct manner from a sample such as blood containing lots of PCR inhibitory substances without undergoing a process of isolating and purifying the nucleic acids, although it has been known that the PCR in the GC rich region is difficult to be conducted even

if purified DNA is used. It becomes possible by the present invention to conduct synthesis of nucleic acids from a sample more simply, conveniently and rapidly. Further, it becomes also possible to reduce contamination. Page 5, lines 12-22.

VI. ISSUES

The issue presented for consideration in this appeal is as follows:

(1) Whether the Examiner erred in rejecting claims 2-3 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite?

(2) Whether the Examiner erred in rejecting claims 1, 2 and 4-9 under 35 U.S.C. §103(a) as being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe")?

(3) Whether the Examiner erred in rejecting claims 3 and 11 under 35 U.S.C. §103(a) as being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe") and further in view of U.S. Patent No. 5,972,618 ("Bloch")?

(4) Whether the Examiner erred in rejecting claim 10 under 35 U.S.C. §103(a) as being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe") and in further view

of Pomp et al., Organic Solvents as Facilitators of Polymerase Chain Reaction," 10 Biofeedback 58 (1991) ("Pomp") and U.S. Patent No. 5,432,065 ("Fuller")?

VII. GROUPING OF CLAIMS

For purposes of this appeal brief only, and without conceding the teachings of any prior art reference, the claims have been grouped as indicated below:

Claims 2-3 stand or fall separately with respect to the §112 rejection.

Claims 1, 2 and 4-9 stand or fall together with respect to the §103 rejections over Henke in view of Watanabe.

Claim 3 and 11 stand or fall together with respect to the §103 rejections over Henke in view of Watanabe and further in view of Bloch.

Claim 10 stands or falls alone with respect to the §103 rejections over Henke in view of Watanabe and further in view of Pomp and Fuller.

In Section VIII below, Applicant has included arguments supporting the separate patentability of each claim group as required by M.P.E.P. § 1206.

VIII. ARGUMENTS

In the Final Office Action of April 9, 2003, the following rejections were presented by the Examiner:

(i) 35 U.S.C. §112

The Examiner rejected claims 2-3 under 35 U.S.C. §112, second paragraph as allegedly being indefinite.

(ii) 35 U.S.C. §103

The Examiner rejected claims 1, 2 and 4-9 under 35 U.S.C. §103(a) as allegedly being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe").

The Examiner rejected claims 3 and 11 under 35 U.S.C. §103(a) as allegedly being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe") and further in view of U.S. Patent No. 5,972,618 ("Bloch").

The Examiner rejected claim 10 under 35 U.S.C. §103(a) as allegedly being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe") and in further view of Pomp et al., Organic Solvents as Facilitators of Polymerase Chain Reaction," 10 Biofeedback 58 (1991) ("Pomp") and U.S. Patent No. 5,432,065 ("Fuller").

(iii) Other

None

For at least the following reasons, Appellant submits that these rejections are both technically and legally unsound and should therefore be reversed.

(i) **35 U.S.C. §112**

The examiner rejected claims 2-3 under 35 U.S.C. §112, second paragraph as allegedly being indefinite. Appellants respectfully disagree, and accordingly, traverse this rejection.

Regarding claim 2, the examiner alleges that "nucleic acid inclusion body" is indefinite because: it is not defined in the claim, the specification does not provide a standard, and there is no fixed definition in the art.

Claim 2 recites a method for synthesis of nucleic acids according to claim 1, wherein a nucleic acid inclusion body from a living body-derived sample or the living body-derived sample itself is added to the amplification reaction solution.

The term "nucleic acid inclusion body" is a compound term based on "nucleic acid" and "inclusion body," the combination referring to the inclusion body (site, location in the cell) for nucleic acid (RNA, DNA) replication. The term is used repeatedly throughout the specification, for example at page 3, line 22, page 8, lines 5, 18 and 21 and page 11, lines 17-18. Appellants believe the term "nucleic acid inclusion body" is clear on its face.

Accordingly, the §112, second paragraph rejection of claim 2 should not be sustained.

Regarding claim 3, the examiner is objecting the examiner alleges that the "and/or" alternative recited in claim 3 is indefinite.

Claim 3 recites a method for synthesis of nucleic acids according to claim 1, wherein said amplifying step comprises adjusting a pH value of the amplification reaction solution to 8.4 or higher if the reaction solution is about 25 °C, and/or adjusting a pH value of the amplification reaction solution to 7.4 or higher if the reaction solution is about 70 °C.

The metes and bounds of claims are not rendered unclear merely because of the presence of alternative language in the claims. The Federal Circuit has held that the word "or"

should be interpreted to mean a choice between one of two alternatives, but not both. See Kustom Signals Inc. v. Applied Concepts Inc., 60 USPQ2d 1133 (Fed. Cir. 2001), cert. denied, 122 S. Ct. 1537 (2002). Expanding on this, it is clear that "and/or" stands for the option of adding the following step to the previous step, or treating the two steps in the alternative. When parsed, Claim 3 clearly recites two situations for adjusting the pH of the amplification reaction solution: 1. adjusting a pH value of the amplification reaction solution to 8.4 or higher if the reaction solution is about 25 °C, and 2. adjusting a pH value of the amplification reaction solution to 7.4 or higher if the reaction solution is about 70 °C. The presence of the coma after the first adjusting language clearly separates the two choices. The phrase "and/or" tells the reader of the claim that choices 1 and 2 can both be performed, or either choice 1 or choice 2 can be performed.

Thus, it is quite clear from the claim, when taken in context, is proper construction, and clear on its face. Accordingly, the §112, second paragraph rejection of claim 3 should not be sustained.

(ii) 35 U.S.C. §103

The Examiner rejected claims 1, 2 and 4-9 under 35 U.S.C. §103(a) as allegedly being obvious over Henke et al., "Betaine Improves the PCR Amplification of GC-Rich DNA Sequences," 25 Nucleic Acids research 3957 (1997) ("Henke") in view of Watanabe et al., "A Reproducible Assay of Polymerase Chain Reaction to Detect Trinucleotide Repeat Expansion of Huntington's Disease and Senile Chorea," 18 Neurological Research 16 (1996) ("Watanabe"). Appellants respectfully traverse this rejection.

Claim 1 recites a method for synthesis of nucleic acids, which comprises: amplifying an intended nucleic acid in a region in which a content of guanine (G) and cytosine (C) is rich in an amplification reaction solution comprising a polyhydric alcohol and ammonium sulfate.

Neither Henke nor Watanabe, alone or in combination, teach or suggest that a polyhydric alcohol and ammonium sulfate are present in an amplification reaction solution together. In fact, it is clear that a person of ordinary skill in the art would not find motivation in

the Henke and Watanabe references to combine their teachings to arrive at such an amplification reaction solution.

Henke essentially teaches away from adding a polyhydric alcohol such as glycerine in some PCR solutions, depending on the nucleic acid to be amplified. Henke teaches (p. 3957) that in a co-amplification of both an antigen's mRNA (GC-rich) and a variant of the antigen's mRNA (also GC-rich) by RT and PCR, 10% glycerine proved ineffective at co-amplification. The amplification of the variant of the antigen's mRNA was optimized when glycerine was added, but the amplification of the antigen's mRNA was depressed. Still further, Henke's PCR process involved isolated gene fragments, and not a more complex nucleic acid inclusion body or an even more complex living body-derived sample. Additionally, Watanabe discloses that genomic DNA was extracted from peripheral lymphocytes (page 17, lines 13 to 14).

Watanabe only makes mention of a PCR process at column 1 of page 17, and column 1 of page 18. In these passages, Watanabe discloses that during a PCR process, 10 mM ammonium sulfate is added to the solution that includes blood samples, and that the ammonium sulfate is greatly effective in terms of improving the efficiency of the process. However, Watanabe clearly fails to teach or suggest the feature of a polyhydric alcohol and ammonium sulfate being present in an amplification reaction solution together.

A person of ordinary skill in the art who reads Henke would actually be steered away from trying to perform PCR using glycerine together with another compound such as ammonium sulfate. Henke teaches that glycerine is not effective at co-amplification PCR, and teaches that betaine improves the co-amplification process when used in place of glycerine. Then, from reading the advantages of using ammonium sulfate in a PCR solution, a person of ordinary skill in the art would, at best, be persuaded to add ammonium sulfate and betaine to a PCR solution for coamplification. However, Watanabe fails to provide any teachings that would overcome a Henke-based presumption that glycerine would be ineffective. When the teachings of the prior art are considered as a whole, there is no motivation found in the references to render claim 1 obvious.

Still further, the Office Action states that Henke and Watanabe "coupled either polyhydric alcohol or ammonium sulfate to the use of DMSO (10%) in an attempt to amplify GC-rich sequences." Page 5, lines 14-15. The examiner then alleges that the "disclosure of each additive's potential for improving the efficiency of PCR involving GC-rich sequences, makes the subsequent combination of such similar, well known additives obvious to one of ordinary

skill in the art." Page 5, lines 16-18. Appellants disagree. As discussed above, if one reference teaches away from using an additive, there can be no obvious working substitution. Still further, this is blatant hindsight reasoning and blueprinting.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, *absent some teaching, suggestion or incentive supporting the combination*. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so. The prior art of record fails to provide any such suggestion or incentive. ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984).

Accordingly, the Examiner has not established a prima facie case of obviousness, the rejection of the claims should not be sustained.

Still further, "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 23 USPQ 2d 1780 (Fed. Cir. 1992). The office action has not established that one of ordinary skill would use ammonium sulfate in place of polyhydric alcohol in Henke. Accordingly, a prima facie case of obviousness has not been established, and the rejection should not be sustained.

The conclusion that this combination would result in the claimed combination is clearly based on Appellants invention and not on the prior art! This form of reasoning is impermissible and is clearly based on improper hindsight reasoning. It is established law that one "cannot use hindsight reconstruction to pick and chose among isolated disclosures in the prior art to deprecate the claimed invention." Ecolochem, Inc. v. Southern California Edison Company, page 23, September 7, 2000 (Fed. Cir.) (citing In re Fine, 837 F.2d 1071, 1075, 5, USPQ2d 1780, 1783 (Fed. Cir. 1988)). "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight." Ecolochem at 24 (citing In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999)). "When a rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references." Ecolochem at 24 (citing In re Rouffet, 149 F.3d 1350, 1355, 47 USPQ2d 1453, 1456 (Fed. Cir. 1988), citing In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987)). Additionally, "defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to

obviousness." Ecolochem at 24 (citing Monarch Knitting Mach. Corp. v. Sulzer Morat Gmbh, 139 F.3d 877, 880, 45 USPQ2d 1977, 1981 (Fed. Cir. 1998)).

Accordingly, a prima facie case of obviousness has not been established, and the rejection should not be sustained.

Furthermore, claims 2 and 4-9, being dependent upon claim 1, are also allowable for the reasons above. Moreover, these claims are further distinguished by the materials recited therein, particularly within the claimed combination. Accordingly, all §103 rejections should not be sustained.

Claims 3 and 11 are rejected as being unpatentable over Henke in view of Watanabe and further in view of U.S. Patent No. 5,972,618 ("Bloch"). Appellants respectfully traverse this rejection.

Claim 3 recites the method for synthesis of nucleic acids according to claim 1, wherein said amplifying step comprises adjusting a pH value of the amplification reaction solution to 8.4 or higher if the reaction solution is about 25 °C, and/or adjusting a pH value of the amplification reaction solution to 7.4 or higher if the reaction solution is about 70 °C.

Claim 11 recites the method for synthesis of nucleic acids according to claim 1, wherein ammonium sulfate is present at a concentration from 20 mM to 100 mM in the amplification reaction solution.

Bloch is provided for teaching an increased pH and concentration of ammonium sulfate in a PCR solution. However, Bloch fails to teach or suggest the use of both ammonium sulfate and a polyhydric alcohol in an amplification reaction solution. Accordingly, Bloch does not make up for the deficiencies of Henke and Watanabe, discussed above. That is, even if the references could be combined, Bloch does not disclose, teach or suggest any teachings that would overcome a Henke-based presumption that glycerine would be ineffective.

Accordingly, a prima facie case of obviousness has not been established, and the rejection should not be sustained.

Furthermore, claims 3 and 11, being dependent upon claim 1, are also allowable for the reasons above. Moreover, these claims are further distinguished by the materials recited

therein, particularly within the claimed combination. Accordingly, all §103 rejections should not be sustained.

Claim 10 was rejected under 35 U.S.C. §103(a) as allegedly being obvious over Henke in view of Watanabe and in further view of Pomp et al., Organic Solvents as Facilitators of Polymerase Chain Reaction," 10 Biofeedback 58 (1991) ("Pomp") and U.S. Patent No. 5,432,065 ("Fuller"). Appellants respectfully traverse this rejection.

Claim 10 recites the method for synthesis of nucleic acids according to claim 7, wherein the aliphatic polyhydric alcohol is ethylene glycol.

Pomp is provided for its teachings of the use of 5 to 20% ethylene glycol in PCR solutions that only used DMSO as an enhancing agent. Since Henke is directed to PCR solutions that could use DMSO, the Examiner's position is that it would be obvious to combine Henke and Pomp to arrive at claim 10. Further, Fuller is provided for its teachings of the use of between 10 and 50% glycerol or ethylene glycol are added to an amplification solution. In any respect, Pomp and Fuller fail to teach or suggest the use of <u>both</u> ammonium sulfate and a polyhydric alcohol in an amplification reaction solution, as recited in claim 1.

Accordingly, Pomp and Fuller do not make up for the deficiencies of Henke and Watanabe, discussed above. That is, even if the references could be combined, Pomp and Fuller do not disclose, teach or suggest any teachings that would overcome a Henke-based presumption that glycerine would be ineffective.

Accordingly, a prima facie case of obviousness has not been established, and the rejection should not be sustained.

Furthermore, claim 10, being dependent upon claim 1, is also allowable for the reasons above. Moreover, this claim is further distinguished by the materials recited therein, particularly within the claimed combination. Accordingly, all §103 rejections should not be sustained.

(iii) **<u>Other</u>**

None

Conclusion

In view of the foregoing reasons, Appellant submits that the final rejection of claims 1-11 is improper and should not be sustained. Therefore, a reversal of the Final Rejection of April 9, 2003, as to claims 1-11, is respectfully requested.

IX. CLAIMS INVOLVED IN THE APPEAL

A copy of the claims involved in the present appeal is attached hereto as Appendix A. As indicated above, the claims in Appendix A do include the amendments filed by Applicant on December 17, 2002.

Dated: September 9, 2003

Respectfully submitted,

By _____

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 180013 for any such fees; and applicant(s) hereby petition for any needed extension of time.

APPENDIX A

Claims Involved in the Appeal of Application Serial No. 09/843,819

1. (Previously presented) A method for synthesis of nucleic acids, which comprises:

amplifying an intended nucleic acid in a region in which a content of guanine (G) and cytosine (C) is rich in an amplification reaction solution comprising a polyhydric alcohol and ammonium sulfate.

2. (Previously presented) The method for synthesis of nucleic acids according to claim 1, wherein a nucleic acid inclusion body from a living body-derived sample or the living body-derived sample itself is added to the amplification reaction solution.

3. (Previously presented) The method for synthesis of nucleic acids according to claim 1, wherein said amplifying step comprises adjusting a pH value of the amplification reaction solution to 8.4 or higher if the reaction solution is about 25 °C, and/or adjusting a pH value of the amplification reaction solution to 7.4 or higher if the reaction solution is about 70 °C.

4. (Original) The method for synthesis of nucleic acids according to claim 1, wherein the GC content in the GC rich region is 40% or more.

5. (Original) The method for synthesis of nucleic acids according to claim 1, wherein the GC content in the GC rich region is a range from 50% to 70%.

6. (Original) The method for synthesis of nucleic acids according to claim 1, wherein the polyhydric alcohol is selected from the group consisting of an aromatic polyhydric alcohol, an aliphatic polyhydric alcohol and an ether glycol.

7. (Original) The method for synthesis of nucleic acids according to claim 6, wherein the aliphatic polyhydric alcohol is selected from the group consisting of ethylene glycol, propylene glycol, butanediol, hexanediol, octanediol, glycerin, sorbitan, trimethylolpropane and neopentyl glycol.

8. (Original) The method for synthesis of nucleic acids according to claim 7, wherein the aliphatic polyhydric alcohol is glycerin.

9. (Original) The method for synthesis of nucleic acids according to claim 8, wherein glycerin is contained in a range from 2.5% to 20% by volume in the amplification reaction solution.

10. (Original) The method for synthesis of nucleic acids according to claim 7, wherein the aliphatic polyhydric alcohol is ethylene glycol.

11. (Original) The method for synthesis of nucleic acids according to claim 1, wherein ammonium sulfate is present at a concentration from 20 mM to 100 mM in the amplification reaction solution.

12. (Cancelled)